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Impact of pre-operative glycated haemoglobin A_{1C} level on 1-year outcomes of endovascular treatment in patients with critical limb ischemia in the course of diabetes mellitus

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Abstract: Introduction: Peripheral arterial occlusive disease (PAOD) is a disease with worldwide increasing occurrence. Diabetic patients are greatly exposed on the risk of PAOD and its complications. The aim of the study was to check the influence of preoperative HbA_{1C} on the outcomes of patients with diabetes undergoing PAOD related endovascular treatment.
Material and Methods: The study was conducted among 59 patients with PAOD referred from the diabetic foot outpatient for endovascular treatment. They were included in one-year observation based on follow-up visits in 1, 3, 6 and 12 months after angioplasty and divided into 2 groups basing on their preoperative glycaemia. The clinical condition of the lower limbs was assessed by use of the Rutherford classification, ankle-brachial index (ABI) and toe-brachial index (TBI). Changes in patients' quality of life (QoL) were also evaluated.
Results: Reintervention within 12 months were less frequent in patients with $HbA_{1C} \leq 8.0\%$ than in $HbA_{1C} > 8.0\%$ patients (9.09% vs. 35.48%, $p = 0.03$). TBI of the treated limb was lower in patients with elevated than in patients with proper glycaemia at 6 month [0.2 (0.0–0.38) vs. 0.38 (0.31–0.46); $p < 0.008$]

and 12 month follow-up [0.17 (0.0–0.27) vs. 0.32 (0.25–0.38); p <0,001]. The rate of healed ulcerations after 6 months was higher in patients HbA_{1C} ≤8.0% (45.0% vs. 16.13%; p = 0.02) and they had significantly greater improvement of QoL.

C o n c l u s i o n: Results of this study shows that preoperative level of glycaemia is an important factor for long-term prognosis in diabetic patients with PAOD. Elevated HbA_{1C} level decreases significantly long-term improvement of QoL in DM patients undergoing endovascular treatment.

Key words: peripheral arterial occlusive disease, diabetes mellitus, HbA_{1C}, quality of life, endovascular treatment.

Introduction

Atherosclerosis with all its complications is one of the most urgent issues in present-day medicine, especially in well-developed countries, and it still remains the leading cause of deaths and disabilities among adults [1, 2]. One of its manifestations is peripheral arterial occlusive disease (PAOD) which occurrence is increasing worldwide [3]. There are multiple PAOD co-factors such as diabetes mellitus (DM), hypertension, hypercholesterolemia, obesity, nicotinism or chronic kidney disease [3–8]. Diabetic patients are one of the most exposed on the risk of PAOD and its complications including incidence as well as its severity [6].

It is believed that 4–10% of patients with diagnosed DM may develop diabetic foot ulcer and their lifetime risk can reach up to 25% [9]. Amputation relative risk among patients with diabetic foot is up to 23.3 times compared to atherosclerotic patients without DM, causing mortality up to 50% depending on studied population and their location [10, 11]. Atherosclerotic lesions can be located in aorto-iliac, femoro-popliteal and below-the knee arteries [12]. In DM patients, great number of the lesions are located in the below the knee arteries (tibial posterior and anterior arteries, fibular and foot arteries) causing the critical limb ischaemia, which often requires endovascular treatment (Percutaneous Transluminal Angioplasty — PTA) [13]. The co-incidence of peripheral arteries disease and DM is also the cause of increase rate of complications such as MACE's and restenosis [14].

In modern vascular medicine, great attention is paid to searching for laboratory parameters that can predict future outcomes of patients undergoing endovascular treatment. [15, 16] The aim of this study was to check the influence of preoperative HbA_{1C} level on the outcomes of DM patients undergoing PTA due to PAOD.

Materials and Methods

Patients

The study, which was a prospective analysis of endovascular procedures registry, was conducted among DM patients administered from diabetic-foot outpatient to Angiology Department for endovascular treatment. Those of them, who were currently undergoing insulin therapy and diagnosed with critical limbs ischemia, were included in this analysis. Basing on the preoperative level of HbA_{1C} patients were dividing into two groups: with HbA_{1C} level ≤8.0% and with HbA_{1C} level >8.0% [17]. Data concerning immediate and distant outcomes of PTA were obtained during one-year observation based on follow-up visits in 1, 3, 6 and 12 months after PTA. The clinical condition of the lower limbs was assessed using the Rutherford classification, Doppler ultrasound, ankle-brachial index (ABI) and toe-brachial index (TBI). The data on Major Adverse Cardiovascular Events was also analysed.

PAOD Diagnostics

PAOD was diagnosed in the angio-CT scan or Doppler ultrasound and confirmed in an angiographic study.

Endovascular Procedures and pharmacology

In all patients, PTA of lower limbs arteries was performed using standard procedures and equipment. During the one-year follow-up, every patient was taking insulin, statins and one or two antiplatelet drugs depending on the stent implantation and type.

Quality of life assessment

Patients recruited to the study were subjected to evaluation of their quality of life (QoL) based on two questionnaires: generic EuroQol-5D (EQ5D-3L) and disease specific Vascular Quality of Life Questionnaire (VascuQol-25). EQ5D contains Visual Analog Scale for general health conditions assessment (higher result represents better QoL) and 5 questions representing domains (if lower result the better QoL): mobility, self-care, daily activities, pain/discomfort and anxiety/depression. VascuQol consist

of 25 questions divided into 5 subscales (higher result represents better QoL): pain, symptoms, activities, social well-being and emotional well-being. Patients were asked to fulfil the questionnaires before the procedure as well as during the follow-up visits.

Endpoints

During all follow-up visits, the clinical condition in the Rutherford scale, need of reintervention due to restenosis or arterial reocclusion and MACE (including death from cardiovascular causes, stroke, myocardial infarction, limb amputation) were evaluated.

Statistical Analysis

The analysis was performed using Statistica software, version 13.0. The results were presented basing on the parameters of descriptive statistics including proportions, mean values and standard deviations, or median values and the corresponding quartiles, as appropriate. In order to confirm a normal distribution, the Shapiro-Wilk test was used. To verify homogeneity of variance the Levene's test was performed. T-student test for homogeneous variances was used to compare nominal variables with continuous variables, which were normally distributed. The comparison of TBI values between patients with different levels of HbA_{1C} was performed with the use of Mann Whitney U test. Chi-square and Fisher's exact tests were applied to compare the categorical variables between the analyzed groups. The significance level was set at 0.05.

Results

In this study 59 patients (18 women and 41 men) were analyzed. Their detailed characteristics were included in Table 1.

Patients with HbA_{1C} level >8.0% had significantly more restenosis causing reinterventions during 1-year observation compared to those with HbA_{1C} ≤8.0% (35.48% vs. 9.09%, p = 0.03). The rate of healed ulcerations after 6 months was lower in patients with HbA_{1C} >8.0% (16.13% vs. 45.0%; p = 0.02), however this phenomena was not statistically significant after 1 year (54.84% vs. 61.9%; p = 0.61). There weren't significant differences in 12-month MACEs (17.14% vs. 16.67%), death (14.29% vs. 8.33%) or amputation rate (19.35% vs. 13.64%) between those groups.

Table 1. Group characteristics.

Number of patients		ALL n = 59 (100%)	HbA_{1C} >8.0 n = 35 (59.32%)	HbA_{1C} ≤8.0 n = 24 (40.68%)	P value
Male [n (%)]		41 (69.49%)	25 (71.43%)	16 (66.67%)	NS
Age [years (±SD)]		68.50 ± 9.579	68.40 ± 9.80	68.65 ± 9.45	NS
Rutherford Scale [n (%)]	4	6 (10.17%)	2 (5.72%)	4 (16.67%)	NS
	5	29 (49.15%)	20 (57.14%)	9 (37.50%)	
	6	24 (40.68%)	13 (37.14%)	11 (45.83%)	
Level of lesion [n (%)]	Aorto-Iliac	3 (5.08%)	1 (2.86%)	2 (8.33%)	0.042
	Fem-Pop	14 (23.73%)	6 (17.14%)	8 (33.33%)	
	BTK	32 (54.24%)	22 (62.86%)	10 (41.67%)	
	Multi-level	10 (16.95%)	6 (17.14%)	4 (16.67%)	
Coronary artery disease		28 (47.46%)	19 (54.29%)	9 (37.5%)	0.039
History of myocardial infarction		15 (25.42%)	10 (28.57%)	5 (20.83%)	NS
History of stroke or TIA		10 (16.95%)	5 (14.29%)	5 (20.83%)	NS
Hypertension		45 (76.27%)	27 (77.14%)	18 (75%)	NS
Chronic kidney disease		17 (28.81%)	9 (25.71%)	8 (33.33%)	NS
Smoking status	Never	10 (16.95%)	6 (17.14%)	4 (16.67%)	NS
	Former	41 (69.49%)	25 (71.43%)	16 (66.66%)	
	Current	8 (13.56%)	4 (11.43%)	4 (16.67%)	
Endovascular procedure	PTA	39 (66.1%)	22 (68.57%)	15 (62.5%)	NS
	PTA + stenting	20 (33.9%)	11 (31.43%)	9 (37.5%)	

TBI of the treated limb was significantly lower in patients with poorly controlled diabetes than in patients with HbA_{1C} ≤8.0 both at 6 [0.2 (0.0–0.38) vs. 0.38 (0.31–0.46); p <0.008] (Fig. 1) and 12 month follow-up [0.17 (0.0–0.27) vs. 0.32 (0.25–0.38); p <0.001] (Fig. 2). Lack of improvement of TBI in 12-months compared to postoperative TBI was more frequent in HbA_{1C} >8.0 patients than in normal HbA_{1C} patients (69.57% vs. 37.5%; p = 0.04). ABI was immeasurable in 57.69% patients with poorly controlled diabetes compared to only 27.78% of normal HbA_{1C} patients.

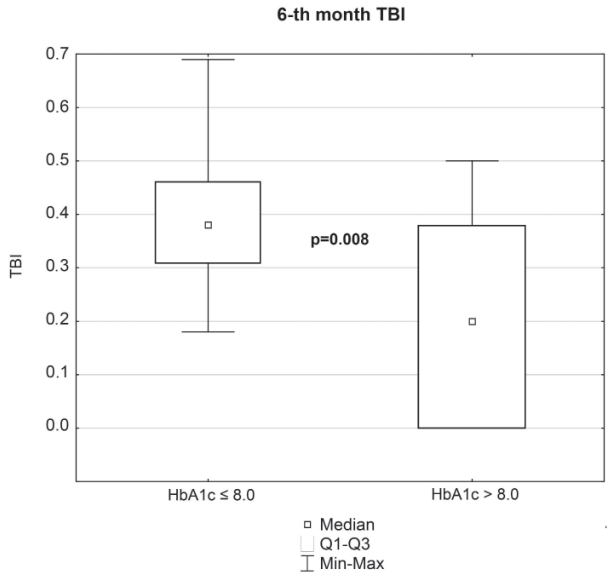

Fig. 1. Difference in toe-brachial index (TBI) between group of patients with HbA_{1C} ≤8.0% and HbA_{1C} >8.0% at 6 month follow-up.

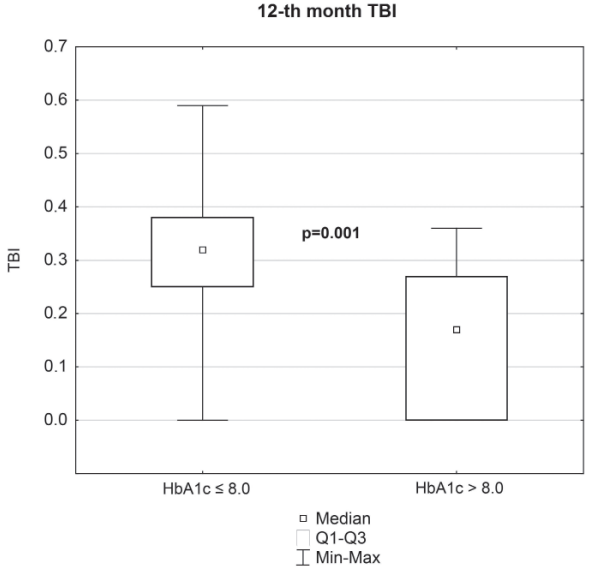

Fig. 2. Difference in toe-brachial index (TBI) between group of patients with HbA_{1C} ≤8.0% and HbA_{1C} >8.0% at 12 month follow-up.

There weren't significant differences in preoperative QoL between both groups of patients, as described in Table 2.

Table 2. Levels of preoperative quality of life assessed by VascuQol and EuroQol-5D questionnaires. In VascuQol higher result represents better life quality, but in EuroQol-5D higher results represents worse life quality (except VAS).

	HbA_{1C} ≤8	HbA_{1C} >8	P
VascuQoL Pre Activity [average (±)]	1.78 (±0.63)	2.02 (±0.95)	0.4703
VascuQoL Pre Symptoms [average (±)]	3 (±1.39)	2.96 (±1.35)	0.8999
VascuQoL Pre Pain [average (±)]	2.66 (±1.7)	2.63 (±1.58)	0.9451
VascuQoL Pre Emotional well-being [average (±)]	2.11 (±0.88)	2.43 (±1.2)	0.4182
VascuQoL Pre Social well-being [average (±)]	2.03 (±1.42)	2.47 (±1.56)	0.3724
EuroQol-5D Mobility [average (±)]	2.47 (±0.62)	2.28 (±0.59)	0.4097
EuroQol-5D Selfcare [average (±)]	1.94 (±0.75)	1.62 (±0.68)	0.1474
EuroQol-5D Daily activities [average (±)]	1.88 (±0.78)	1.96 (±0.79)	0.7363
EuroQol-5D Pain [average (±)]	2.29 (±0.69)	2.28 (±0.65)	0.8997
EuroQol-5D Anxiety [average (±)]	1.65 (±0.79)	1.79 (±0.62)	0.3682
EuroQol-5D VAS [average (±)]	46.47 (±18.35)	51.43 (±15.57)	0.5829

Differences in quality of life changes (12-month vs. preoperative) between groups were observed in all 5 domains of VascuQol, however only 3 of them were statistically significant (symptoms, pain and emotional well-being) (Fig. 3). Results of EQ5D-3L presented significant differences in QOL changes only in mobility domain (Fig. 4). Patients with HbA_{1C} ≤8.0% had significantly higher rate of life quality improvement in 4 out of 5 VascuQol-25 domains (activities: 88.2% vs. 53.8%, p = 0.019; symptoms: 88.2% vs. 50.0%, p = 0.010; emotional well-being: 94.1% vs. 65.4%, p = 0.029; social well-being: 82.3% vs. 46.2%, p = 0.018). In pain domain rate of improvement had the same tendency however there was no statistical significance (70.6% vs. 42.3%, p = 0.069).

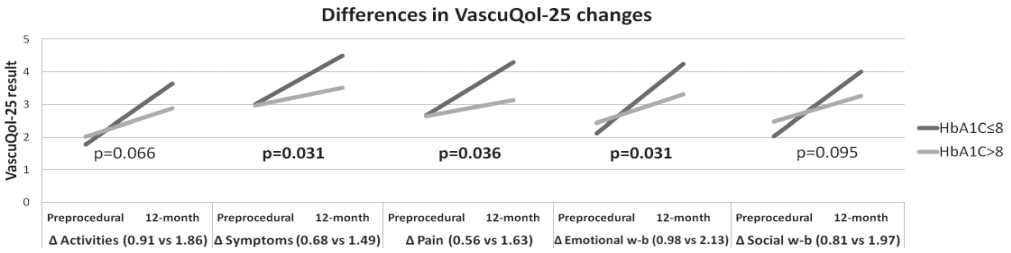

Fig. 3. ΔVascuQol-25 in each of 5 domains compared between patients with HbA_{1C} ≤8.0% and HbA_{1C} >8.0%. Higher result represents better quality of life in all 5 domains.

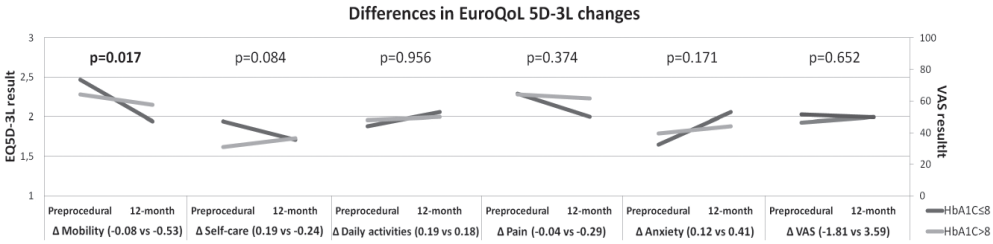

Fig. 4. ΔEuroQol 5D-3L in each of 5 domains and VAS compared between patients with HbA_{1C} ≤8.0% and HbA_{1C} >8.0%. Lower result represents better quality of life in all 5 domains. In VAS higher result represent better QoL.

Discussion

Results summary

Patients with HbAC1 ≤8.0% have better TBI results in 6 and 12-month observation after PTA (Fig. 1 and Fig. 2). They also present lower rate of restenosis and higher rate of healed ulcerations. Quality of life, especially regarding activities, symptoms, emotional well-being and social well-being, improved more frequent and the improvement was greater.

Role of glycaemia control in atherosclerosis management

It has been proven in multiple studies that properly controlled glycaemia plays crucial role in both short- and long-term outcomes of DM patient's treatment [18–20]. In *2019 Guidelines on the management of diabetic patients* was stated that HbA_{1C} should be kept ≤8.0% "in patients at an advanced age and/or in diabetics with macroangiopathic complications […] and/or multiple comorbidities" [17]. Elevated HbA_{1C} level is one of the most important factors on atherosclerosis progression and trigger factor for its complications [21, 22]. According to Iren Drange Hjellestad *et al.* "HBA_{1C} results may identify persons at high risk of long-term mortality following surgical treatment for PAD" [22]. Recent study conducted by Shipra Arya *et al.* shows that elevated preoperative glycaemia in patients undergoing endovascular treatment or vascular surgery have higher probability of limb amputation and/or MACEs [23].

Quality of life

The aspect of quality of life is often overlooked, but it is one of the most important outcomes of any treatment, especially in chronic diseases. Following other studies design we decided to cover patients with 2 different types of QoL

questionnaires [24–26]. As the results show, the EQ5D-3L did not gave many significant dependences, which is due to its nature — this questionnaire is a generic one and may be less useful is small study groups. Vascuqol-25 questionnaire provided us with much important information, even if some dependence did not presented the statistical significance, they kept the same trend and possibly the significance would be stronger if the population was bigger. However one of the negative results raised our concern — the rate of patients with improvement in pain domain did not significantly differ between groups. In our opinion this can be explained by the fact that patients with DM often suffer from diabetic peripheral neuropathy, which may be lowering the sense of pain [27]. Our hypothesis is supported by the fact, that patients with proper glycaemia who reported improvement in pain feeling showed bigger difference in this domain compared to those with elevated HbA_{1C} (Fig. 3).

ABI and TBI measurements issues

Although described new methods, ABI as a non-invasive, low-cost measurement is one of the most common methods of proper lower limbs blood circulation assessment [28]. Unfortunately it often tends to be less accurate in patients suffering from DM due to arteries calcifications [29, 30]. That is why in this study full analysis of ABI measurements was not performed, however rate of ABI immeasurability has been checked. There is no objective or standardized definition of neither TBI nor ABI improvement or worsening. Both of those parameters should be assessed accompanied by patients' symptoms and their general condition. Basing on our experience, for the purpose of this study we defined the improvement of TBI as $\Delta \geq 10\%$ or $\Delta < 10\%$ but within the normal range (TBI ≥ 0.74) [31].

Clinical outcomes controversies

Our results did not confirm the higher rate of amputations and MACEs in patients with higher preoperative HbA_{1C} described by Shipra Arya *et al.* [23], which probably was caused by low number of those events observed. Difference in rate of ulcerations healed was significant, but only in 6-month observation and was not present in 1-year observation. The reason for this phenomena was that patients with unhealing wounds and restenosis (whose number was greater in $HbA_{1C} > 8.0$ group) were often undergoing reinterventions after 6-month improving the healing of ulcerations in next months.

Study limitations

The main limitation of this study is modest sample size, which were only 59 patients. The subject of influence of increased preoperative HbA_{1C} on long term outcomes

after endovascular procedures and open vascular surgery have been explored by big studies, however the novelty of this study is based on the assessment of quality of life changes in patients during 1-year observation [21, 23]. What is more we analyzed more homogenic group, as all of patients included in this study were diabetics, undertaking insulinotherapy and undergoing only endovascular treatment. To perform the complete analysis the confounding factors need to be balanced as well as multivariable analysis should be performed. Also calculation of 5 or 10 years survival rate would be beneficial for the study. Another, minor limitation is lack of complete data on presence of neuropathy in studied patients. Concluding all those mentioned limitations, there is clear need for long-lasting prospective study with larger sample size to confirm our results.

Conclusions

Results of this study show that the level of HbA_{1C} is an important factor of long-term prognosis in diabetic patients with critical limb ischemia. Elevated level of HbA_{1C} negatively affects the life quality improvement in diabetic patients subjected to PTA of the lower limbs arteries in long-term observation.

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Conflict of interest

None declared.

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